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(54) Title: PROCESS USING THE GROWTH FACTOR IGF–I IN THE MANUFACTURE OF COMPOSITIONS THAT ARE USEFUL IN THE TREATMENT OF CEREBELLAR ATAXIA

(57) Abstract

Process using the growth factor IGF–I in the manufacture of compositions that are useful for the treatement of cerebellar ataxia. The invention which is claimed is a treatment for curing experimental ataxia which, because of the characteristics of the animal model used, may turn out to be useful in human beings. Ataxia is a neurological deficit for which there is no cure at present. The application of the IGF–I composition is by peripheral administration, which eliminates all the complications derived from the intracerebral administration which has been carried out until now for growth factors in the treatment of brain diseases. The effects obtained from the administration of IGF–I can also be achieved by the administration of compositions that increase the circulating levels thereof, for example compositions containing GHRH and/or GH.

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PROCESS USING THE GROWTH FACTOR IGF-I IN THE MANUFACTURE OF COMPOSITIONS THAT ARE USEFUL IN THE TREATMENT OF CEREBELLAR ATAXIA

TECHNICAL SECTOR

The invention relates to the technical sector of the preparations based on neurotrophic factors of natural origin, more specifically IGF-I and the use thereof in the manufacture of pharmaceutical compositions that are useful in the treatment of neurological diseases, particularly in the treatment of cerebellar ataxia.

PRIOR ART

The treatment of neurological diseases with neurotrophic factors of natural origin has recently been the subject of a large number of studies (F. Hefti. Neurotrophic factor therapy for nervous system degenerative diseases. J. Neurobiol. 25, 1418-1435, 1994). To date only partially successful results in animal models in which a relative improvement in the disease is achieved have been published. As recent representative examples we can cite the use of the CNTF factor in motoneurone degeneration models (J. D. Rothstein. Therapeutic horizons for amytrophic lateral sclerosis. Curr. Op. Neurobiol. 6:679-687, 1996), of the NGF factor in the treatment of diabetic neuropathies in rats (S. B. McMahon, J. V. Priestley. Peripheral neuropathies and neurotrophic factors: animal models and clinical perspectives. Curr. Op. Neurobiol. 5:616-624, 1995) or of FGF-2 for the attenuation of the intellectual deficits associated with aging (A. Baird. Fibroblast growth factors: activities and significance of non-neurotrophin neurotrophic growth factors. Curr. Op. Neurobiol. 4:78-86, 1994). In all these cases the administration of the growth factor is intracerebral, which makes its application in human beings enormously difficult.

The use of the factor IGF-I as a therapeutic factor in various diseases has had controversial results, but in any

case some uses have already been authorized by organizations such as the US FDA (Federal Drug Administration). Others are in the course of being authorized. To date only its use in Laron-type dwarfism has given a clearly positive result (Z. Laron, S. Anin, Y. Klipper-Aurbach, B. Klinger. Effects of insulin-like growth factor on linear growth, head circumference, and body fat in patients with Laron-type dwarfism. Lancet 339: 1258-1261, 1992). Its use in amyotrophic lateral sclerosis has just been authorized by the FDA for clinical trial phase (J. D. Rothstein, Therapeutic horizons for amyotrophic lateral sclerosis. Curr. Op. Neurobiol. 6:679-687, 1996). Tolerance to IGF-I appears good and is free from major side effects. The therapeutic use of this product is by continuous peripheral subcutaneous administration.

Taking into account the fact that the recovery from Ataxia in the experimental model is directly correlated with the plasma levels of IGF-I and that the administration of GH both subcutaneously and intramuscularly causes a well-known increase in circulating IGF-I levels (Copeland et al. 1980, Hynes et al. 1987), the invention also extends to the administration of GH (growth hormone) and GHRH, which is the hormone that physiologically stimulates growth hormone (Rochiccioli et al. 1987), and specifically GHRH(1-29) NH_2 (both the latter product and GH being marketed by Serono), in this disease and all the possible applications thereof:

- Rochiccioli P.E., Tamber M.T., Coude F. X., Arnone M., Morre M., Ubaldi F., Barbeau C. Results of 1 year GHRH (1-44) treatment on growth, somatomedin-C and 24 hour GH secretion in 6 children with partial GH deficiency. J. Clin. Endocrinol. and Metab. 65:268-274 (1987).
- Copeland K.C., Underwood L.E., Van Wyk J.J. Induction of immunocreative Som-C in human serum by GH. Clin. Endocrinol. Metab. 50:690-697 (1980).
- Hynes M.A., Van Wyk J.J., D'Ercole A.J., Jansen M., Lurd P.K. GH dependence of som-C/IGF-I and IGF-II messenger RNA. Mol. Endocrinol. 1:233-242 (1987).

Cerebral ataxia is a neurological syndrome with various origins (spontaneous, hereditary, drug-acquired, etc.) and with a relatively low incidence compared with other neurological diseases (2/100,000 in Spain, although it is much higher in other countries. J. Berciano. Olivopontocerebellar atrophy. In: "Parkinson's disease and movement disorders. Pages 163-189. Williams and Wilkins (1993). There is no type of treatment, however, either palliative or curative, and the patients (of any age) have a very poor quality of life and eventually die because of the lack of muscle movements in the glottis or lungs. It is a slow degenerative disease with a high social cost. For all these reasons there is an urgent need for treatment of any kind.

DESCRIPTION OF THE INVENTION

BRIEF DESCRIPTION OF THE INVENTION

The continued treatment of ataxic animals with peripherally administered IGF-I (continuous subcutaneous infusion) completely cures the failure of motor co-ordination of these animals. The cure is permanent, as after suspension of the treatment the animals remain normal and do not show any side effects on glucose metabolism.

DETAILED DESCRIPTION OF THE INVENTION

The treatment which we have devised for this disease consists of the continuous peripheral administration of IGF-I (Total dose of 200 μg of IGF-I by subcutaneous implantation of an osmotic minipump; the equivalent in human beings would be a skin patch or an insulin-type pump). In our animal model of ataxia a complete cure is obtained after a month, allowing the treatment to be suspended as the neurons which usually die because of the disease are permanently restored by this growth factor. The cure of the animals was measured by motor skill tests in a "Rota-rod" apparatus (Ugo Basiles) developed for this purpose, and 98% normalization of the

parameters was obtained. The untreated animals only have 2-4% of the normal levels of motor coordination, which in practical terms means that they are unable to make movements which are simple for a healthy rat to perform. A second motor skill test, known as the "inclined platform" test, gave the same type of positive result. All these results are statistically significant ($p<0.001$ vs. ataxic control animals). Other ways of determining the cure in the animals were: 1) electrophysiological recording of the neuronal connections, which are lost in the ataxic animals and are completely recovered in the animals treated with IGF-I: ataxic animals have 20% correct connections, intact normal animals have 98%, and the animals treated with IGF-I have 82%, 2) in addition, by anatomical analysis of the neuron population affected in the ataxic animals it was determined that in the latter the number of neurons surviving is less than 20% of the normal neuron population, whereas the animals treated with IGF-I keep more than 80% live neurons compared to the control animals ($p<0.001$).

EXEMPLARY EMBODIMENT OF THE INVENTION

Deafferentation is performed on experimental animals in order to cause ataxia (difficulty in co-ordinating muscle movements). IGF-I is continuously administered subcutaneously until total recovery of the co-ordination of movements is achieved; the degree of ataxia of the treated animals has to be monitored weekly for this purpose. As soon as they are cured the treatment is suspended, as the cure is permanent, the neurons responsible for controlling the movements are cured by IGF-I and do not die.

CLAIMS

1. Process using the growth factor IGF-I in the manufacture of a composition to be administered in the treatment of cerebellar ataxia.

2. Process according to Claim 1, characterised in that the IGF-I composition is administered by means of a subcutaneously implanted osmotic minipump.

3. Process according to Claims 1 and 2, characterised in that the total dosage of the IGF-I composition to be administered is 200 μg.

4. Process using GHRH, particularly GHRH(1-29)NH_2 and/or GH, in the manufacture of a composition which increases circulatory IGF-I levels and is useful in the treatment of cerebellar ataxia.

5. Process according to Claim 4, characterised in that the GHRH, particularly GHRH(1-29)NH_2 and/or GH, composition is administered subcutaneously or intramuscularly.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/30 A61K38/27 A61K38/25

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,O	FERNANDEZ, A. M. ET AL: "Insulin - like growth factor modulates functional recovery in a rat model of cerebellar ataxia." MEETING INFO.: 27TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE NEW ORLEANS, LOUISIANA, USA OCTOBER 25-30, 1997, see the whole document -& SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 23, no. 1-2, 1997, page 1451 XP002102591	1-3
Y	--- -/--	4,5

[X] Further documents are listed in the continuation of box C.

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X Y	US 5 633 228 A (LEWIS MICHAEL E ET AL) 27 May 1997 see abstract see column 1, line 66 - column 2, line 14 see column 2, line 39 - line 42 see column 9, line 10 - line 56 see claims 1-3	1-3 4,5
Y	US 5 492 891 A (SKAKKEB K NIELS E ET AL) 20 February 1996 see abstract see column 1, line 53 - line 67 see claims 1-3	4,5
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